REMARKS

This invention relates to one-step immunoassays to detect extracted analytes. These assays permit efficient extraction of analytes from samples, while minimizing manipulation of the treated sample following extraction. Avoiding manipulation of the sample following extraction permits these assays to be performed by individuals without extensive training in laboratory techniques.

In addition, these assays permit control over the extent and duration of the extraction procedure. By carrying out extraction of a sample in an assay chamber which is not in flow contact with the sample receiving region of the immunoassay test strip, lateral flow of the treated sample through the test strip is not initiated until the sample receiving region of the immunoassay test strip is inserted into the treated sample. Insertion of the immunoassay test strip into the treated sample avoids manipulation of the treated sample, for instance, by pipetting the treated sample onto the sample receiving region of the test strip.

This control over initiation of the lateral flow permits greater control over mixing of the sample with the extraction reagents, as well as greater control over the duration of the mixing and extraction procedure. This added control over extraction conditions, thus permits, greater efficiency of extraction and thereby increases the sensitivity of the assay.

Moreover, because the extraction is performed in a separate assay chamber, these assays do not require a complex plastic or cardboard housing or specially designed swabs to fit in the complex housings to help control flow of the sample from the sample chamber portion of the housing to the sample receiving region of the

immunoassay test strip. Other methods for the detection of treated samples which attempt to minimize sample manipulation after sample treatment make use of sample extraction chambers which are in flow contact with the immunoassay test strip and which contain bulky and/or specialized housings. These bulky and/or specialized housings are necessary to prevent free flow of the extraction buffer to the sample receiving region of the test strip matrix, *i.e.*, by designing a sample receiving/extraction area of the device to fit snugly around a sample swab where the sample receiving area is in flow communication with the sample receiving region of the test strip. Even so, some extraction buffer begins flowing onto the test strip sample receiving region of the test strip as soon as the buffer is added to the extraction area in flow communication with the test strip.

Furthermore, when using a separate assay chamber, two sample extraction reagents can be used, and they may be added to the assay chamber in any order, permitting these assays to be performed by individuals without extensive training.

Claims 10-20 are pending. Claims 10-11, 13-15, and 17-20 have been rejected as anticipated by Imrich et al. (U.S. Patent No. 5,415,994) (hereinafter "Imrich"). Claims 12 and 16 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Imrich et al. in view of Bogart et al. (U.S. Patent No. 5,494, 801) and Murray (U.S. Patent No. 3,957,436).

35 U.S.C. § 102

The Examiner has rejected claims 10-11, 13-15, and 17-20 as anticipated by Imrich. Applicant respectfully traverses this rejection. Imrich fails to teach a separate sample chamber which is not in flow communication with the test strip; as a result,

Imrich does not describe elements of steps (b), (c) and (d) of claim 10: "(b) providing an assay chamber; (c) extracting said antigen from said sample with an extraction solution comprising one or two extraction regents in said assay chamber, wherein said one extraction regent is added to the assay chamber, to form a liquid extract, or wherein said two extraction reagents are added to said assay chamber in any order, to form a liquid extract; (d) inserting said sample receiving region of said lateral flow immunochromatographic device into said assay chamber and contacting said liquid extract."

The Imrich device does contain a structure termed an "extraction chamber," but the Imrich "extraction chamber" cannot be used as a chamber to extract a sample for a controlled period of time, because the sample flows out the exit port of the sample receiving area. This is true whether the two halves of the Imrich device are separated or assembled. Moreover, Imrich contains no disclosure of how the sample could be extracted in the "extraction chamber" while the device is dissembled, nor is there any suggestion to first extract the sample in the "extraction chamber" of a dissembled device and then to transfer the extracted sample to the sample receiving region of the immunoassay test strip in the bottom half of the disassembled device. There is also no suggestion to first extract the sample in the "extraction chamber" of a dissembled device and to then assemble the device to bring the sample into contact with the test device, especially since the sample would be free to flow out of the exit port of the "extraction chamber."

Although Imrich contains qualifying language stating that "generally" the devices of Imrich may contain an extraction chamber (Imrich at Col. 2, line 26), or that the

immunoassay test matrix is conveniently" located in a solid casing, Imrich does not describe the use of immunoassay devices other than those containing an extraction chamber in an plastic housing. In addition, although the housing of the exemplary Imrich device is manufactured in a two-step procedure, during operation the top and bottom halves of the Imrich device are sealed together. "Generally, there are two plastic components in the device. The top piece contains the sample processing features; the bottom piece is used for strip placement. The top and bottom components are constructed so that a press fit secures the assembly." Imrich at Col. 7, ll. 37-41. In addition, in the Imrich device, the immunoassay test strip, *i.e.*, a "matrix", is in flow connection with the sample receiving area termed the "extraction chamber," because the extraction chamber has a hole, *i.e.*, the "exit port" at the bottom through which extraction buffer can flow to the immunoassay test strip. At Column 2, lines 27-28, in the summary of the invention, Imrich specifies that the matrix defining an axial flow path (*i.e.*, the test strip) is "in fluid connection with the extraction chamber." Imrich further states that "[t]he extraction chamber is fluidly connected to the matrix by means of an exit port located distally in the chamber." Imrich at Col. 4, ll. 25-27. "Conveniently, the matrix is contained within a solid casing. The extraction chamber is formed as an integral part of the top of the solid casing. An exit port fluidly connects the extraction chamber to the sample receiving zone of the matrix." Imrich at Col. 7, ll. 11-15.

Thus, when assembled, and in use as described, the Imrich device's sample receiving area is in flow communication with the test strip via the "exit port." Flow through the exit port in the bottom of the extraction "chamber" to the sample receiving region of the test strip can begin as soon as extraction buffer is added to the sample

receiving region and the test strip is not inserted into the sample receiving area to initiate lateral flow. "In this embodiment, the sample may be placed in the extraction chamber and treated with the extraction solution to prepare the analyte for detection. The extraction solution will carry the treated analyte to the sample receiving zone on the matrix." Imrich at Col. 7, ll. 17-22.

Accordingly, in Imrich, the immunochromotagraphic test strip matrix is in flow communication with the sample chamber, which has an exit port through which treated samples flow during use. Because the extraction solution flows through the exit port (either directly or through a filter), Imrich does not disclose "inserting said sample receiving region of said lateral flow immunochromatographic device into said assay chamber and contacting said liquid extract whereby said liquid extract flows through said labeling situs and then through said capture situs without further addition of reagents or manipulation of said sample," as required in step (d) of claim 10.

Imrich therefore cannot anticipate claim 10, because it does not disclose every element of that claim. *See Applied Medical Resources Corp. v. United States Surgical Corp.*, 147 F.3d 1374, 47 U.S.P.Q.2d (BNA) 1289 (Fed. Cir. 1998), *cert. denied*, 119 S. Ct. 870 (1999) (affirming jury verdict of no anticipation where prior art did not disclose every element of the claimed invention even though the prior art device possessed identically named parts, where the identically named parts did not have the same structure or otherwise meet the claim limitations).

Thus, Imrich cannot anticipate claims 11, 13-15 or 17-20. Claims 11, 13-15 and 17-19 are dependent on claim 10, and therefore include the limitations of step (d). In addition, claim 20 also recites step (d) which requires "inserting said sample receiving

region of said lateral flow immunochromatographic device into said assay chamber and contacting said liquid extract whereby said liquid extract flows through said labeling situs and then through said capture situs without further addition of reagents or manipulation of said sample." Thus, Imrich does not anticipate any of the pending claims 10-20.

35 U.S.C. § 103

Claims 10-20

Applicants further respectfully assert that claims 10-20 would not be obvious in light of Imrich.

The Federal Circuit has recently reiterated that there must be a motivation or suggestion to combine elements from different prior art references, and that it is improper to use hindsight reconstruction and an assumed level of general knowledge in the art to provide this motivation in order to reach a conclusion of obviousness. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1323-24, 50 U.S.P.Q.2d (BNA) 1161, 1170 (Fed. Cir. 1999):

> VSI is unable, however, to point to any specific teaching or suggestion for making this combination. VSI instead relies on what it presumes is the level of knowledge of one of ordinary skill in the art at the time of the invention to supply the missing suggestion to combine. In the first place, the level of skill in the art is a prism or lens through which a judge or jury views the prior art and the claimed invention. This reference point prevents these deciders from using their own insight or, worse yet, hindsight, to gauge obviousness. Rarely, however, will the skill in the art component operate to supply missing knowledge or prior art to reach an obviousness judgment. See *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 20 USPQ 303, 312-13 (Fed.Cir.1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."). Skill in the art does not act as a bridge over gaps in substantive

> presentation of an obviousness case, but instead supplies the primary guarantee of objectivity in the process. *See Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718, 21 USPQ2d 1053, 1057 (Fed. Cir. 1991).

Al-Site, 174 F.3d at 1324. Moreover, an invention is not unpatentable because it was "obvious to try." *In re O' Farrell*, 853 F.2d 894, 902, 7 U.S.P.Q.2d (BNA) 337 (Fed. Cir. 1988).

Here, as discussed above, Imrich describes only the use of devices containing both the immunoassay test strip and an extraction chamber with an exit port, in fluid communication with the immunoassay test strip matrix. Imrich does not describe or suggest a method for detecting a Strep A antigen where the assay chamber is separated from the immunoassay device and the immunoassay device is inserted into the assay chamber to initiate lateral flow. Moreover, because the bulky devices used in Imrich would not easily fit within assay chambers which would permit efficient extraction, there is no suggestion from the disclosure of Imrich to one of ordinary skill in the art to insert the immunochromatographic device into the extracted sample in an assay chamber. February 26, 1999 Schwartz Decl. at ¶¶ 7, 10.

As discussed above, in the instant method, however, spatial separation of the assay chamber from lateral flow contact with the sample receiving region of the test strip until after the test strip is inserted into the extracted sample, permits greater control over the length and efficiency of extraction, and hence, the sensitivity of the assay. February 26, 1999 Schwartz Decl. at ¶¶ 4, 7.

The Examiner has indicated that the Schwartz declaration's references to the housing and overall sensitivity of the Strep A assay carried out with the OSOM™ device are not relevant to the individual claims of the instant application. Office Action at ¶ 5.

Applicants respectfully disagree. In the Schwartz declaration, Dr. Schwartz notes that the OSOM™ Strep A test carried out using the OSOM™ device is exemplary of a method which would fall within claim 10. February 26, 1999 Schwartz Decl. at ¶ 3.

Moreover, although the OSOM™ Strep A test device is an example of one device suitable for inserting into a sample chamber and a bulky device such as the one described in Imrich would not be able to fit in a sample chamber small enough to obtain efficient extraction, the increased sensitivity of the claimed assays do not result from the exact configuration of the device. The lack of a bulky housing in the test performed using the OSOM™ device, however, does permit the claimed inserting step, step (d) to be performed, and thereby eliminates the need for further manipulation of the sample.

The overall sensitivity of the device is dependent in large part on controlling the time for sample extraction, which cannot be as carefully regulated in a device which has the sample chamber in flow communication with the matrix. (February 26, 1999 Schwartz Decl. at ¶¶ 5-6). In such a device, some of the extraction buffer will immediately begin flowing through the exit port onto the sample receiving region of the matrix. (February 26, 1999 Schwartz Decl. at ¶ 6).

Dr. Schwartz's comments regarding the sensitivity of the OSOM™ device are relevant to the claimed invention because the claimed steps of providing a separate assay chamber and inserting the immunochromatographic test device into the assay chamber to initiate lateral flow, permits efficient extraction of the samples and hence, greater sensitivity. (February 26, 1999 Schwartz Decl. at ¶¶ 4, 7). Thus, the increased sensitivity of exemplary assays performed with the OSOM™ device helps to establish the advantages of the claimed method over the prior art.

Applicants therefore respectfully assert that none the claims of the instant invention are obvious in view of Imrich.

Claims 12 and 16

The Examiner has rejected claims 12 and 16 as unpatentable over Imrich et al. in view of Bogart et al. (U.S. Patent No. 5,494,801) and Murray (U.S. Patent No. 3,957,436).

Taken together, Imrich, Bogart, and Murray (U.S. Patent No. 3,957,436) do not teach a method for determining the presence or absence of a Streptococcus antigen, where a separate assay chamber is provided and lateral flow of the immunoassay is initiated by inserting the immunochromatographic device into the extracted sample, where the extraction solution comprises 0.2-5M sodium nitrite and 0.02-2M acetic acid, or where the solution contains a color indicator to indicate proper preparation. As discussed above, Imrich fails to teach or suggest a method for the detection of an analyte where the immunoassay test strip is not in flow communication with the extraction chamber, and where a separate assay chamber is provided and lateral flow of the immunoassay is initiated by inserting the immunochromatographic device into the extracted sample. In addition, as noted at page 10 of the Office Action mailed September 2, 1998 in the parent application, Imrich does not teach vigorous mixing of the swab and extraction reagents for at least 10 seconds, or an extraction solution where the addition of 0.3 M acetic acid to a color-indicator spiked 2 M sodium nitrite solution changes the color of the final extraction solution.

Applicants therefore respectfully assert that the claimed invention is not obvious in light of Imrich et al., either alone or in combination with Bogart and/or Murray.

CONCLUSION

For the reasons set forth above, Applicants believe that claims 10-20 clearly state that the claimed invention is directed to a method for detecting a Streptococcus antigen where an immunoassay device, and a separate assay chamber are provided. The claims also clearly state that the immunoassay device is inserted into the assay chamber after completion of extraction of the sample. Moreover, Applicants respectfully assert that the claims are not anticipated nor made obvious by Imrich, which describes only methods using devices in which the immunoassay test strip is in uninterrupted flow communication with the extraction chamber, a separate assay chamber is not provided, and the immunoassay test strip matrix is not inserted into the extracted sample to initiate flow. Applicants thus believe that the claims are in condition for allowance.

Respectfully submitted,

LYON & LYON LLP

Dated: November 12, 1999

By: Vicki G. Norton

Vicki G. Norton
Reg. No. 40,745

Library Tower
633 West Fifth Street, Suite 4700
Los Angeles, California 90071-2066
Tel: (858) 552-8400
Fax: (213) 955-0440